

Friday, October 30, 1981

COM-1
~~46 FR 5370~~

**ENVIRONMENTAL PROTECTION
AGENCY**

40 CFR Part 799

[TSH-FRL-1973-6; OPTS-42002]

**Fluoroalkenes; Response to the
Interagency Testing Committee**

AGENCY: Environmental Protection
Agency (EPA).

ACTION: Advance notice of proposed
rulemaking.

SUMMARY: Section 4(e) of the Toxic
Substances Control Act (TSCA)
established an Intragency Testing
Committee (ITC) to recommend to the
Administrator of the Environmental
Protection Agency (EPA) a list of
chemical substances and mixtures to be
considered for the development of test
rules under TSCA section 4(a). On
November 25, 1980 notice appeared in
the Federal Register that the ITC
recommended the category,
fluoroalkenes, for health effects testing.
EPA is publishing this Advance Notice
of Proposed Rulemaking under section
4(e) of TSCA to (1) Inform the public of
the rationale to be used in selecting the
chemicals for testing; (2) define the
testing it is considering proposing; and
(3) seek public comment on these plans
to propose test rules.

DATE: Written comments should be
submitted on or before December 29,
1981.

ADDRESS: Please address your
comments to: Document Control Officer,
Management Support Division (TS-793),
Office of Pesticides and Toxic
Substances, Environmental Protection
Agency, 401 M St., SW., Washington,
D.C. 20460.

FOR FURTHER INFORMATION CONTACT:
John B. Ritch, Jr., Director, Industry
Assistance Office (TS-799), Office of
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Washington, D.C. 20460, toll free: (800-
424-9085), in Washington, D.C. (554-
1404), outside the USA: (operator-202-
554-1404).

SUPPLEMENTARY INFORMATION:

I. Background

A. ITC Report

Section 4(a) of TSCA authorizes the
Administrator of EPA to promulgate
regulations requiring testing of chemical
substances and mixtures in order to
develop data relevant to determining the
risks that such chemicals may present to
health and the environment.

Section 4(e) of TSCA established the
ITC to recommend to the Administrator

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of EPA those chemicals that should receive priority consideration for proposed test rules under section 4(a). The Committee may at any one time designate up to 50 of its recommendations for special attention by EAP. Within 12 months of that designation, EPA must initiate rulemaking to require testing or publish in the Federal Register reasons for not doing so.

The ITC transmitted its Seventh Report to the Administrator of EPA, as published in the Federal Register of November 25, 1980 (45 FR 78432), and its recommendations included the category, fluoroalkenes, for consideration. The fluoroalkenes were recommended for human health effects testing.

The fluoroalkene category is defined as fluoroalkenes of the general formula:



where n equals 2 or 3 and x equals 1 to 6. EPA has identified from the confidential and public portion of the TSCA Chemical Substances Inventory six fluoroalkenes meeting the category definition. This category currently includes the six fluoroalkenes shown below. However, should additional chemicals be identified which meet the category definition, these will be added to and considered with this action.

Chemical	CAS No.
Tetrafluoroethene (TFE)	116-14-3
Trifluoroethene	359-11-5
Vinylidene fluoride (VDF)	75-38-7
Vinyl fluoride (VF)	75-02-6
Hexafluoropropene (HFP)	116-15-4
Trifluoropropene (TFP)	677-21-4

Chemicals in this category are used primarily in the synthesis of polymers and copolymers with high resistance to heat and corrosion. The usage patterns of the polymers, e.g., in the automotive industry and in pollution control, would indicate an increasing demand for these chemicals (West and Holcomb 1979).

In its report, the ITC recommended testing of appropriate members of this category for mutagenicity, carcinogenicity, for teratogenic and reproductive effects, and for chronic health effects with particular emphasis on the renal and cardiovascular systems. The category was not recommended for environmental effects or environmental fate studies.

B. Scoping Workshop

To facilitate TSCA section 4 activities, the Agency held a scoping workshop for fluoroalkenes and other 7th ITC list chemicals on March 12, 1981. Notice of the workshop was published in the Federal Register on February 13, 1981 (46 FR 12317-12323). In this notice, industry representatives, academic

experts, labor, environmental groups, and the general public were invited to meet with EPA staff to discuss the issues which EPA needed to resolve in order to respond to the ITC Report. Specific questions indicating EPA's major concerns were published in the notice to serve as guides for the discussion.

At the scoping workshop, industry representatives presented views on production levels and exposure potential in their plants, and statements about the type of monitoring carried out, detection limits, and action taken when detectable levels are recorded. In addition, they stated that reports on acute toxicity testing of tetrafluoroethene and teratogenicity of vinylidene fluoride were available and that protocols for subacute and subchronic testing of tetrafluoroethene would soon be available for Agency review. These studies will be done by DuPont. Evaluations of research needs were presented by academic experts.

The manufacturers of four of the chemicals in this category formed a consortium in the weeks following the workshop, and this group, called the Fluoroalkene Industry Group (FIG), submitted reports on exposure to vinyl fluoride, vinylidene fluoride, tetrafluoroethene and hexafluoropropene. DuPont, a member of the FIG, has also independently submitted to EPA two sets of protocols and one acute study report on fluoroalkene category chemicals including:

1. Protocol for testing vinylidene fluoride for carcinogenicity and chronic toxicity in rats (Maltoni laboratories) (DuPont 1981c).
2. Protocol for testing tetrafluoroethene for acute, subacute, and subchronic inhalation toxicity in rats and hamsters (Haskell laboratories) (DuPont 1981b).
3. Report on the LC₅₀ of tetrafluoroethene in hamsters (Haskell laboratories) (DuPont 1981a).

II. Response of EPA to ITC Report

EPA has reviewed the ITC report, the available data on which the recommendation was based, the information obtained at, or subsequent to the scoping workshop, and information obtained from EPA's own information-gathering activities. The Agency in general accepts the recommendations of the ITC that members of the fluoroalkene category be considered for testing for carcinogenicity, mutagenicity, teratogenicity, reproductive effects and other toxic effects. The basis for these views is presented later in this notice.

EPA had previously indicated that although it would generally initiate testing action through publication of a proposed rule, it would initiate action on chemical categories and certain complex chemicals through publication of an Advance Notice of Proposed Rulemaking (ANPR), as it is doing in this case. There are several reasons, both general to categories and specific to the fluoroalkenes, why the Agency has chosen to apply this policy.

The Agency has found that in attempting to develop formal rulemaking for a category, the issues which require attention are more complex and numerous than in rulemaking for a single chemical and thus require more time.

In order to avoid unnecessary or duplicative testing, while assuring that adequate data are developed, the Agency attempts to determine whether it is scientifically valid to test one or more representative chemicals rather than to test each chemical individually. One method of achieving this goal is through the use of structure-activity relationships (SAR), a field which is on the frontiers of science. Although SAR for the fluoroalkenes is not well documented, the Agency believes that there is a logical basis for pursuing SAR along the lines proposed in this notice (i.e., subcategorization according to placement of the fluorine and length of the carbon atom chain). However, to arrive at this level of decision was a labor-intensive effort involving review of data on SAR and conceptual application of SAR theory to this category. In addition to review of SAR data, the data on the individual fluoroalkenes need to be identified and then compared using SAR principles. Of course, development of structure-activity analysis is only part of the effort necessary for development of a proposed testing rule for a category. In addition, in this case EPA must review data applicable to exposure, release, and unreasonable risk (including consideration of costs of testing and economic impact) for six chemicals, instead of the one which would be required if ITC nominated a single chemical for testing. Furthermore, while EPA could conduct its preliminary analysis of these data in parallel with its structure-activity efforts, EPA could not proceed to make the legal findings for the category (or subcategories) until the results of the structure-activity work indicated whether and how the individual chemicals in this category were to be grouped for testing purposes. EPA believes that it would generally be impossible to complete these findings to

allow publication of a proposed rule, in whatever time would be available after completion of the structure-activity analysis.

In addition to the difficulty EPA has in preparing a proposed rule on a category such as this, EPA believes that there are positive advantages in using an ANPR to initiate the process of testing a category of chemicals. Publication of such a notice provides an opportunity for public comment on the difficult issues involved in use of structural categories, before the Agency expends its resources on developing proposed test rules on those categories. Proceeding with the development of full-blown rules prior to receiving such input could result in a waste of the Agency's limited resources if the categorical approach was modified as a result of comment, because the Agency might then have to reconsider the bases of many of its test findings.

III. General Information

A. Chemical Description

Members of the category are all gases at room temperature with boiling points ranging from -18°C for trifluoropropene to -82°C for vinylidene fluoride. They are highly volatile and moderately degradable in the atmosphere, reacting with ozone, hydroxyl radicals and atomic oxygen to cleave the double bond or form addition products. All the chemicals are essentially insoluble in water. Vinyl fluoride and vinylidene fluoride are flammable over wide ranges of concentration, and are explosive at concentrations of 2.6-21.7 percent and 5.5-21.3 percent by volume respectively.

Production of vinyl fluoride is achieved by addition of hydrofluoric acid (HF) to acetylene with pyrolysis of the product to the unsaturated structure. Vinylidene fluoride is produced by treating the reaction product of HF and acetylene, $\text{C}_2\text{H}_2\text{CHF}_2$, with chlorine and heat to produce the unsaturated difluoride. Similar reactions are followed for the production of the other members of the class (Kirk-Othmer 1979).

B. Manufacturing Process and Exposure Potential

The following description of the vinyl fluoride manufacturing process is taken from a NIOSH survey report (NIOSH 1977) and from reports provided by DuPont, the sole manufacturer of vinyl fluoride, through the Fluoroalkene Industry Group (FIG 1981a). Descriptions of the processes for production of vinylidene fluoride, tetrafluoroethene, and hexafluoropropene also provided by Fluoroalkene Industry Group (FIG 1981b,c) indicate similar operating procedures are in effect at the plants

where these chemicals are manufactured. Corresponding information is not available for the other two chemicals.

According to the NIOSH survey report (NIOSH 1977) on the sole vinyl fluoride manufacturing plant, primary control is by enclosure of the process materials under pressure. Leakage from the process equipment, piping and storage is reportedly held to a minimum but can occur. When excess pressures occur, the gases are vented through the top of the process tower to the atmosphere. Environmental exposure from this source has not been evaluated.

Polymerization takes place in high pressure polymerization vessels which are located in separate areas behind barrier walls. Chemical process technicians (operators) are housed in a separate control building and are not allowed in the process area during manufacture. Operators wear self-contained emergency air supply respirators in the processing area when a serious leakage problem exists. Respirators with canisters capable of removal of organic vapors and acid gases are used routinely by plant operators while performing tasks in the processing areas of the plant after manufacture operations are shut down. The operators of the processing plant are expected to have the greatest potential for exposure. Maintenance and management personnel and chemists may have occasional, incidental exposures. NIOSH stated that the existing operational control procedures and the resulting exposure levels appear to be consistent with good practice and, in view of the toxicological information, adequate for the prevention of adverse health effects. Acute effects are not expected at these or even higher levels. However, chronic effects are not well defined in relation to long-term exposure to low concentrations (NIOSH 1977).

The NIOSH Industrial Hygiene Survey for vinyl fluoride (NIOSH 1977) included an exposure measurement during maintenance operations while the production plant was shut down as well as during start-up operations. Exposure measurements subsequent to plant start-up are considered to be indicative of the normal operating conditions for vinyl fluoride production operations. No measurements were made during on-stream maintenance or repair. On-stream maintenance or repair work may result in substantially higher short-term exposures than routine operational exposure.

When an unscheduled breakdown does occur, the area is purged of vinyl fluoride before maintenance personnel

are permitted near any of the equipment, until monitoring shows levels below 3 parts per million (ppm). All personnel involved in a breakdown are required to wear air-supplied respirators (FIG 1981a).

The results of the survey for a full 8-hour shift personal sample during plant start-up indicated an operator exposure of 21 ppm vinyl fluoride (time weighted average or TWA), and subsequent personal samples and area samples during the two successive eight hour shifts indicated air concentrations to average less than 2 ppm (TWA) vinyl fluoride, the threshold limit value (TLV).

C. Estimate of Worker Exposure to Fluoroalkenes

The Fluoroalkene Industry Group (FIG 1981b) reports that an estimate of the total number of persons potentially exposed to vinylidene fluoride is 460 persons. This includes all production, maintenance, laboratory, and packaging employees in the monomer and polymer processes at the DuPont and Pennwalt plants as well as at processing plants of Pennwalt's customers. The FIG also reports that the total number of workers exposed annually in manufacturing the vinyl fluoride monomer and in processing it to the polymer is 100 (FIG 1981a). The estimate for tetrafluoroethene is 750 workers, and for hexafluoropropene it is 785 workers (FIG 1981c). NIOSH reports, however, that 1400 employees are potentially exposed to vinyl fluoride at the DuPont plant surveyed, of which 25 operators, 10 foreman, and 4 supervisors were engaged in production of vinyl fluoride for about half the plant's production time (NIOSH 1977).

Halocarbon Products, Incorporated, which is the sole producer of trifluoroethene and one of two producers of trifluoropropene, estimates a total of one-half person-year of exposure to the former and five person-years of exposure to the latter chemical (Halocarbon 1981). However, actual numbers of employees potentially exposed have not been provided.

The Agency is also aware that nearly seven million pounds of vinyl fluoride are transported annually in closed tanks by rail from DuPont's production plant in Louisville, Kentucky to its processing facilities in Buffalo, New York (FIG 1981a). The Agency estimates this represents between 2600 and 4400 cars per year (Folden 1981) which presents a potential for additional exposure of workers in case of a derailment, leak, or spill.

IV. Tentative EPA Decisions and Issues

A. Development of Rulemaking

EPA, after analysis of the comments on the ITC report and after review of the data presented at the scoping workshop, believes that there is reason to proceed with development of a proposed rule for testing of the fluoroalkenes.

EPA in publishing the ANPR wishes to receive early comment on its tentative basis for requiring testing, on the use of subcategories, and on the tests the Agency believes necessary to characterize the effects of the fluoroalkenes. The bases for the use of subcategories, for the suggested findings, and for the tests under consideration are discussed below.

B. Decision on the Use of Sub-Categories

The designation of a category is intended by the ITC to allow simultaneous consideration of a group of chemicals. The use of such tools as structure-activity relationships (SAR), in which biological effects of one compound can be inferred from another because of similar chemical structures and/or reactivities, has been suggested for facilitating testing proposals for categories.

In order to facilitate the choice of which chemicals to test within the category, EPA is proposing a subcategorization approach: the members of each subcategory should share structure-activity relationships based on the number and location of the fluorines substituted for hydrogen on the carbon atoms of the molecules. This approach was initially set forth by industry participants at the scoping workshop.

At the scoping workshop, discussions focused on the use of three subcategories for testing. These are listed below:

Subcategory A—Vinyl Fluoride and Vinylidene Fluoride

Subcategory B—Trifluoroethene, Tetrafluoroethene and Hexafluoropropene

Subcategory C—Trifluoropropene

The structural relationship of the members of each subcategory can be described chemically as follows: Subcategory A contains compounds with one or two fluorines substituted on one of the vinyl carbons while subcategory B contains compounds with three or more fluorines substituted for the hydrogens on the vinyl carbons as well as on the alpha carbon. Subcategory C contains only 1,1,1-trifluoro-2-propene which is unlike the other compounds because none of its fluorines are attached to the double-bonded carbon. It reacts more like propylene than the other category members, as predicted from the fact that

vinyl halides react differently from alkyl halides (Cook and Pierce 1973). Vinyl fluoride and vinylidene fluoride (subcategory A) are similarly unreactive, while tetrafluoroethene and hexafluoropropene (subcategory B) tend to be fairly reactive (Clayton 1977). The reactivity of trifluoroethene is not established relative to the other subcategory B compounds, but is expected to be similar.

For the purpose of deciding which compounds should be tested, EPA would expect to propose testing of one chemical from each of the first two subcategories. Such testing would establish the effects for a compound with few fluorines and for one with many fluorines.

The third subcategory needs to be dealt with separately. Production and exposure figures are very low for trifluoropropene, and there is little indication of potential health effects other than some neurotoxic effects reported in conjunction with testing large doses of the compound for possible use as an anesthetic (Robbins 1948). EPA would expect to drop consideration of this compound for testing.

In general, EPA would expect to consider the data available on each compound for each health effect to determine which of the members of a subcategory should be chosen for testing. EPA assumes SAR is valid for these compounds within the subcategory, thereby obviating the need for testing each member of the category for each effect.

C. Preliminary Findings

1. *Potential hazard and exposure.* The Agency considers that the fluoroalkenes meet the criteria for a finding under section 4 (a) (1) (A) (i); that "the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment." This belief is based on evidence of adverse health effects which might pose an unreasonable risk to health. Adverse health effects include carcinogenic effects demonstrated for vinylidene fluoride, pre-neoplastic (carcinogenic) lesions with vinyl fluoride, positive mutagenic potential for vinylidene fluoride and vinyl fluoride, demonstrated renal function impairment for tetrafluoroethene and hexafluoropropene, and potential cardiovascular effects for tetrafluoroethene, trifluoroethene, vinylidene fluoride, vinyl fluoride and

hexafluoropropene. The five compounds for which effects have been demonstrated, i.e. all except trifluoropropene, share a close structural relationship. It is assumed that common structural features would behave similarly in chemical reactions, differing mainly in degree or rate of reaction. This assumption is acceptable to validate use of the method to identify health hazards. Such identification is necessary in order to propose a section 4 (a) (1) (A) finding for a chemical related to one for which effects have been demonstrated. The Agency believes that testing is needed to gather the data for all members of the category except possibly trifluoropropene.

The finding is also based on the fact that these chemicals are being produced under conditions which suggest that long-term exposure potential could exist. Should additional data be submitted which indicate that exposure levels are insignificant and numbers of people exposed are very low for all of the chemicals within the category, the Agency would reconsider its decision to proceed with this testing action. EPA will in the intervening period between ANPR and NPR attempt to refine the exposure data and reconsider its decisions in light of data available for the NPR.

2. Adequacy of information and need for testing.

a. *Oncogenicity.* The ITC cited a report of carcinogenic effects of vinylidene fluoride in rats (Maltoni 1979). The ITC evaluated the study in question and concluded that certain features were questionable. EPA concurs with this conclusion. EPA's analysis of the Maltoni study concluded that deficiencies in the design of the study must be resolved. These deficiencies were as follows: (1) the data were pooled for lipomas and liposarcomas when calculating the statistical significance of the results; (2) too few test animals were used; and (3) the use of intubation for volatile solvents introduces uncertainty about the interaction between the test compound, vinylidene fluoride, and the diet.

Other studies showing potentiation of premalignant hepatocellular lesions by vinylidene fluoride (Stockle et al. 1979) and liver toxicity of vinyl fluoride (Conolly and Jaeger 1977; Conolly et al. 1978) taken together with the first study raised sufficient concern that the Committee recommended testing of fluoroalkenes for carcinogenicity. The comments at the scoping workshop indicated that a group of producers would be retesting vinylidene fluoride using the inhalation route of exposure.

These studies (including a complete range-finding subchronic study) are to commence this coming January. The work will be performed by Dr. Maltoni (DuPont 1981c). The Agency has reviewed the draft protocol for this retest and finds it generally satisfactory. As a consequence, the Agency does not expect to propose oncogenic testing of vinylidene fluoride. It is also the Agency's view that the oncogenic potential of vinyl fluoride will generally be ascertained by the vinylidene fluoride test to be performed, because there is a clear similarity of genotoxic test results for the two substances, most of which were positive. Therefore, in accordance with the decision to select only one chemical from each subcategory for testing, EPA would expect to propose that these test results be considered valid evidence of vinyl fluoride's carcinogenic potential, and that any ultimate regulatory decision based upon vinylidene fluoride's oncogenicity extend to vinyl fluoride as well.

In addition, the Agency would expect to propose testing of one compound from subcategory B, based upon the overall similarities of the category, in order to fully evaluate the carcinogenic potential of the category.

b. *Mutagenicity.* The ITC reviewed mutagenic (Ames test) studies of vinyl fluoride, vinylidene fluoride, tetrafluoroethene and hexafluoropropene. Results of vinyl fluoride and vinylidene fluoride testing for mutagenicity were positive in two studies and negative in one. Hexafluoropropene and tetrafluoroethene gave negative results. The ITC recommended short-term tests to assess the genotoxic effects of members of the category because of the inconsistencies in these studies. EPA's preliminary judgment is that further mutagenic testing is necessary.

At the scoping conference, industry participants discussed plans to run such tests voluntarily. The Agency will work with FIG to develop a suitable voluntary test program, or will propose section 4 test rules if that cannot be accomplished. If voluntary testing is not initiated in the near future, the Agency would expect to require lower tier mutagenicity testing of all chemicals in subcategories A and B to determine the SAR relationship and mutagenic activity.

c. *Teratogenic and reproductive effects.* The ITC recommended testing for teratogenic and reproductive effects based on the absence of reported studies and the expected biological activity of members of the category. No reports have been found in the literature

of any teratogenic or reproductive studies for these six substances. Pennwalt Corporation submitted a report at the scoping workshop giving negative results for teratogenic testing of vinylidene fluoride at 10,000 ppm in rats (Pennwalt 1981). A review by agency scientists indicates that this study will be acceptable as evidence for lack of teratogenicity. Because the fluoroalkenes are being proposed for testing under TSCA section 4(a)(1)(A), "unreasonable risk", no further testing will be required unless additional information is supplied to the Agency after the publication of this ANPRM which indicates that fluoroalkenes are of concern for teratogenic risk.

d. *Other toxic effects.* In conjunction with studies showing a wide variation in acute inhalation toxicity of fluoroalkenes, tetrafluoroethene and hexafluoropropene were reported to impair renal function in rats. Other studies showed that the five category members included in subcategories A and B were metabolized when inhaled by male rats. The ITC cited a report which stated that release of fluoride ion can occur during metabolism of fluoroalkenes. This ion affects the kidney, causing potassium depletion which may eventually affect the cardiovascular system. ITC recommended that members of the category be tested for chronic health effects with particular emphasis on renal and cardiovascular effects.

The Agency believes that there is an adequate basis for concern about chronic effects of these five substances. The Agency believes that a properly conducted 90-day study will be an adequate surrogate for a full chronic effects study, because the effects of concern are not age-related and should therefore be observed in a 90-day study. With respect to vinylidene fluoride the Agency believes that the Maltoni oncogenicity study should be capable of providing sufficient information regarding chronic effects. Therefore, EPA does not plan to require an additional subchronic study on subcategory A-chemicals but believes it should require subchronic testing of a subcategory B chemical.

e. *Environmental effects.* EPA agrees with the ITC evaluation and does not expect to propose environmental testing at this time, based on the available data on physical-chemical properties, reported LC₅₀'s and degradation rate.

V. References

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VI. Development Schedule

The Agency wishes to receive scientific discussion on all aspects on

the use of SAR for this particular category. It will reconsider its position if data and logic indicate that the decision to test using subcategories based on structure-activity relationships is erroneous.

The Agency will analyze all comments on categorization, SAR relationships, exposure, production and use of available data received from this ANPR. The Agency will also accept any voluntary testing plans submitted for review and comment. These testing plans need not be final for inclusion in the ANPR comments, but should be formal protocols for proper review. All of the above will be included in the public record and will form the basis of the NPR or Decision Not to Test. EPA is planning to publish the NPR not later than October 1982.

(Sec. 4, 90 Stat. 2003; (15 U.S.C. 2601))

Dated: October 23, 1981.

Anne M. Gorsuch,

Administrator.

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